continuation application and new claims 19 to 21 have been added. Accordingly, amended claims 1, 4, 5, 7, 8, 12, 17 and new claims 19 to 21 presently are under examination.

The amended specification and claims as well as the addition of the new claims are fully supported by the original disclosure. By this Amendment, the specification has been amended to identify trademarks as requested by the Examiner. Claims 1, 5, 8 and 12 have been amended to "consisting essentially of" rather than the transition term "comprising" and the insertion of specific nucleotides at specific positions. Support for the insertion of these nucleotides can be found in SEQ ID 15 and 29. Also by this amendment, claims 13 and 14 have been canceled; these method claims are now the subject matter of new claims 19 and 20. Claim 18 has been replaced by new claim 21. Accordingly, support for new claims 19 through 21 is found in originally filed claims 13 and 14 and later filed claim 18.

The amendments to the specification and claims do not raise an issue of new matter and entry thereof is respectfully requested.

In view of the preceding amendments and the remarks that follow, Applicants respectfully request that the Examiner reconsider and withdraw the objections to the specification and the rejections of the claims set forth in the outstanding Office Action.

A. INFORMATION DISCLOSURE STATEMENT

The Examiner stated that the information disclosure statement filed in connection with this application has not

been entered because no copy of the abstract of Herlocher et al., abstract of Castucci, article by Kilbourne or article by WHO was provided. A substitute information disclosure statement will be filed along with the requested references for the Examiner's consideration and entry into the application file.

B. OBJECTIONS TO THE SPECIFICATION

In paragraph 3 of the Office Action, the Examiner objected to the specification on the ground that trademarks were not properly identified. In accordance with the Examiner's request, the specification has been amended to identify trademarks. Removal of this objection is respectfully requested.

In paragraph 4 of the Action, the Examiner objected to the specification on the ground that the accession numbers of the wild-type and cold adapted strain were not provided. In response to this objection, Applicants direct the Examiner's attention to page 1 of the Preliminary Amendment filed July 22, 1993 wherein the specification was amended to insert the ATCC accession numbers for each of the wild-type strain and the ca strain. Accordingly, reconsideration and removal of this objection is respectfully requested.

C. 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 4, 5, 7 to 8, 12 to 14, 17 and 18 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter sought to be patented.

The Examiner questioned in paragraph 5a if the nucleic acids of the claims comprise only those sequences or other sequences of genes. The Examiner also noted that the claims were in an improper Markush format.

In response to the Examiner's rejection but without conceding the correctness thereof, the claims have been amended to remove Markush format and to recite "consisting of" rather than the transition term "comprising". The amended claims are not open ended; they clearly indicate that Applicants intend as their invention the sequences set forth by the recited sequence ID number.

In paragraph 5b, the Examiner further objected to claims 4 and 7 on the ground that the use of the term "complementary" was allegedly vague and indefinite.

In response, Applicants direct the Examiner to page 5, lines 19 to 22 of the specification wherein it states that "[i]t will also be appreciated that although the viruses of the present invention are RNA viruses, the present invention further includes DNA sequences corresponding and complementary thereto." "Complementary" is known to those of skill in the art to mean "a sequence of polynucleotides related by the base-pairing rules. For example, in DNA a sequence A-G-T in one strand is complementary to T-C-A in other strand. A given sequence defines the complementary

sequence." *A Dictionary of Genetics* King and Stansfield, eds., Oxford University Press (1990) p. 71 (copy enclosed). Thus, it would be clear to one of skill in the art reading the claims in light of the specification that claims 4 and 7 are intended to encompass DNA complementary stands to the RNA nucleic acid molecules defined by the specific sequences identified by their sequence ID numbers.

In paragraphs 5c through 5e, the Examiner objected to the claims on the grounds that: 1) it was unclear what the metes and bounds of the claims are because "operatively linked" is unclear; 2) it is unclear to the Examiner whether Applicants only intend the surface proteins NA and HA; 3) "isolated nucleic acid" was open ended; and 4) "nucleic acid" does not clearly identify that the nucleic acids defined by the recited sequences are RNA or DNA.

Without conceding the correctness of the Examiner's position and merely to place the claims in condition for allowance, the claims have been amended to either of sequence ID numbers 15 or 29 and to specifically recite "HA and NA". Applicants point out that the claimed nucleic acids are RNA sequences (see pages 92 and 128 of the application papers which clearly indicates that the term "nucleic acid" does not encompass DNA). With respect to the use of the term "operatively linked" Applicants direct the Examiner to page 5, lines 30 to 32 wherein the term is defined as "attached or assembled in a manner which allows for expression of the surface and internal genes."

In view of the amendments to the claims and the preceding clarification, Applicants respectfully request

that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

D. 35 U.S.C. § 112, FIRST PARAGRAPH

The specification was objected to and claims 1, 4, 5, 7-8 and 12 to 18 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an enabling disclosure.

In his remarks, the Examiner recognizes that the elected species is to nucleic acids and reassortant viruses containing a nucleic acid coding for at least one surface antigen of the wild-type and a nucleic acid coding for PB2 of the cold adapted virus. However, the Examiner opines that the specification fails to enable the scope of the claims because it appears from the prior art that more than HA, NA and PB2 is required for effectiveness. The Examiner also questioned the animal model used by Applicants. The Examiner further questioned the efficacy of the various reassortants that are encompassed by the claims.

Applicants respectfully traverse for the reasons which follow. First, Applicants point out that although the Examiner's rejections are deemed to be a failure to satisfy 35 U.S.C. § 112, first paragraph, his remarks in support of the rejection are directed to the efficacy of the claimed invention (35 U.S.C. § 101, operability or utility). Failure to satisfy 35 U.S.C. § 112, first paragraph is a failure to teach one of skill in the art how to make and use the invention of the claims. The Examiner has not indicated in his remarks how Applicants have failed to teach one of

skill in the art how to make and use the invention of the claims. Rather, the Examiner questions the operability of the inventions encompassed by the claims by commenting on the failure of the scope of the invention to work for its intended purpose and the animal model to predict efficacious vaccination in humans. In other words, the Examiner questions the operability of the claimed inventions.

Therefore, because the Examiner appears to rejecting the claims under 35 U.S.C. § 101, Applicants will separately address the satisfaction of this statutory provision.

Applicants have enabled the scope of the invention by teaching one of skill in the art how to make and use the inventions of the amended claims. The sequence information provided by Applicants allows one of skill in the art to reproduce the sequences of amended claims 1, 4, 5, 7, 8, 12 and new claims 19 to 21. The specification also teaches one of skill in the art how to make and use reassortant viruses and vaccine preparations in the

following experimental examples as summarized below:

	Experiment:	Findings:
Example 1	Sequencing of all 8 genes of the *ca* and *wt* variants of the A/AA/6/60 strain.	Comparison between the two sequences shows 9 base changes in the entire genome. 5 cause amino acid changes, the others are silent in terms of protein sequence. Two silent mutations are on PB2 (corresponding to SEQ 15 in the *ca*, SEQ 29 in the *wt*). The mutation at position 1933 of PB2 may be important in the ability of RNA to survive in the cold, because it is expected to cause a cascade of 163 paring differences in the RNA fold.
Example 2	Sequence comparisons with: 1. GenBank sequences of other influenza strains; 2. Previously published work by Cox et al. with other *ca* and *wt* variants of the A/AA/6/60 strain.	Many previously described differences between *ca* and *wt* are probably either neutral differences or differences that arise as a result of adaptation to the cell line used for propagation. The 141 and 1933 bases of PB2 are consistently mutated in *ca* variants.
Example 3	General procedure for developing *reassortants:* Cold-adapted viruses, comprising elements of the *ca* master strain, and the *wt* epidemic strain against which an effective vaccine is desired.	29 reassortants listed for Type A influenza. 7 reassortants listed for Type B influenza. Type A reassortants were created using the *ca* variant of A/AA/6/60.
Example 4	General procedure for growing sufficient quantities of the reassortant to create a vaccine pool, and measuring infectivity titers.	
Example 5	General procedure for testing production lots of the vaccine, comprising phenotypic evaluation, genotypic evaluation, and ferret reactogenicity.	

Example 6	Results of clinical studies in over 20,000 people, from 4 months to 80 years old.	Table 10 shows that 10 different *ca* vaccines of either Type A or Type B were *all attenuated, antigenic, genetically stable, and effective.*
Example 7	Results of studies to determine the effect of vaccinating with several *ca* adapted influenza strains simultaneously.	Simultaneous administration may generate slightly lower titers than sequential administration, but an effective dose can be determined for using all 3 together.
Example 8	Procedure for introducing point-mutations into cold adapted influenza virus, such as introducing the temperature sensitive mutation from A/Leningrad.	
Example 9	Proposal to use *ca* viruses of the invention as a viral vector for the development of other vaccines.	It enables the introduction of immunogenic epitopes from several different influenza strains into the HA and NA surface proteins of a *ca* virus. This would provide a single-component vaccine against multiple strains. It enables the introduction of epitopes from other viruses, such as HIV.
Example 10	Procedure for conducting clinical studies on influenza vaccines, such as the one reported in Example 7.	

With respect to the use of the ferret model as an animal model, Applicants submit that to satisfy the utility requirement for patentability, an animal model need only be the accepted model in the art field. The ferret model is the accepted model in this field.

The Examiner also remarked that the claimed invention encompasses a reassortant virus that could contain the surface antigen of influenza B with the PB2 gene of the Type A virus.

Applicants respectfully respond that one of skill in the art using the teaching of the specification is enabled for the production of such virus.

In view of the preceding amendments to the claims and remarks, Applicants respectfully request that the Examiner reconsider and withdraw the grounds for rejection of the claims set forth in paragraphs 6 through 8.

The Examiner also rejected claims 15 and 16 on the ground that the inventions thereof are not enabled without a deposit of the ca and wt influenza strains. Applicants have canceled these claims without prejudice thereby rendering this rejection moot.

In view of the preceding amendments and remarks, Applicants respectfully request that the Examiner reconsider and withdraw the grounds for rejecting the claims under 35 U.S.C. § 112, first paragraph.

E. 35 U.S.C. § 102

Claims 15 and 16 were variously rejected under various provisions of 35 U.S.C. § 102. However, because Applicants have now canceled these claims without prejudice, these grounds for rejecting the claims are moot.

F. 35 U.S.C. § 102/103

Claims 1, 4 and 18 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. § 103, as allegedly obvious over Buonagurio et al. Applicants traverse these rejections for the reasons which follow.

Claim 1 is directed to the nucleic acid sequence consisting essentially of the sequence shown in ID 15, further characterized as consisting of guanine at nucleotide 821 and cytosine at position 1933. Claim 4 is directed to a DNA sequence which is complementary to the sequence of claim 1. Claim 18 has been canceled without prejudice and new claim 21 has been added. Claim 21 is directed to an isolated nucleic acid sequence comprising at least one of the following sequences: SEQ ID 1, 3, 5, 7, 9, 11, 13, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, and 39 and an isolated nucleic acid sequence consisting essentially of SEQ ID 15 and the isolated nucleic acid sequence of SEQ ID 15 further characterized as consisting of guanine at nucleotide 821 and cytosine at position 1933.

Applicants reassert that the invention of claims 1 and 4 is not anticipated or obvious over Buonagurio et al. Buonagurio et al. does not anticipate or render obvious the claims because it fails to disclose the sequence of the isolated PB2 segment of the virus nor enable one to reproduce it either by providing the sequence or a readily available deposit.

Claims 1, 4, 5, 7, 8, 12, 13, 14, 17 and 18 stand rejected under 35 U.S.C. § 103 for allegedly being obvious over Cox et al., in view of Belshe et al. (May 1994) or Belshe et al. (April 1992). Applicants traverse.

The claims are non-obvious over the prior art because the primary reference, Cox et al. does not teach or suggest Applicants' isolated PB2 segment of the virus. Thus, because the sequence of the segment is different, Cox et al. does not teach or suggest Applicants' claims. Therefore, Cox et al. does not enable Applicants' claimed invention and accordingly, does not render it obvious. The secondary references of Belshe et al. do

not provide the deficiencies present in the primary reference. Specifically, none of Cox et al. or Belshe et al. (1984 or 1992) enable the isolated PB2 nucleic acid sequence of this invention. Accordingly, the claims are non-obvious over the combination of Cox et al. in view of Belshe et al. (1984) and Belshe et al. (1992). Applicants respectfully request that these grounds for rejecting the claims under 35 U.S.C. § 103 be removed.

G. CONCLUSION

If a telephone interview would be of assistance in advancing prosecution of this application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 03-1952. However, the

Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

By Antoinette F Konski
Antoinette F. Konski
Registration No. 34,202

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MORRISON & FOERSTER
755 Page Mill Road
Palo Alto, CA 94304-1018
(415) 813-5600
Fax: (415) 494-0792